REMARKS

Restriction Requirement

The Examiner has maintained the Restriction Requirement. Applicants have cancelled claims directed to non-elected inventions, with the exception of the method claims of Group V, which the Examiner has indicated could be considered for rejoinder pending allowance of claims in Group I. Applicants expressly reserve the right to pursue the subject matter of the non-elected claims in a divisional application, without the need to file a terminal disclaimer.

Declaration

The Examiner has stated that the inventors' Declaration is defective. Enclosed herewith is a substitute Declaration pursuant to 37 CFR 1.67(a).

Drawings

The Examiner has objected to the drawings as being difficult to understand due to the poor quality of copies. Applicants submit herewith formal drawings of better quality in which the bars in the graph have different patterns so that the figure can be properly viewed. With regard to Fig. 2, for example, it is submitted that one can now distinguish between "One Cell" and "Two (+) Cells." The Examiner is respectfully requested to withdraw this objection.

Objection to the Specification and Rejection of Claim 4 Under 35 U.S.C. § 112, First Paragraph

The Examiner has objected to the specification and rejected Claim 4 under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner contends that the specification fails to provide any teachings of how to produce a protein that is encoded by a nucleic acid molecule that hybridizes to the nucleic acid molecule encoding the same protein.

Applicants assume that the Examiner was indicating that Claim 4 should recite a nucleic acid molecule that hybridizes to *the complement* of a nucleic acid molecule encoding FGF-2. However, to address the concerns under 35 U.S.C. § 112, second paragraph discussed below, Applicants have removed the reference to stringent hybridization conditions. The specification supports this amendment on page 17, line 11 to page 19, line 3; page 13, lines 11-27; and page 15, lines 12-27. Applicants submit that the specification describes the protein in Claim 4, as amended, and combined

with the knowledge in the art, teaches one of skill in the art how to identify and/or produce the protein as presently claimed in Claim 4 by both structure and function.

Therefore, the Examiner is respectfully requested to withdraw the rejection of Claim 4 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1-18 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 1-18 under 35 U.S.C. § 112, second paragraph, for several reasons.

First, Claim 1 is rejected as allegedly being unclear with regard to the phrase "in the absence of heparan sulfate. Applicants have amended Claim 1 to clarify that the FGF chimera has FGF biological activity that occurs in the absence of heparan sulfate. As discussed in the specification (see page 9, lines 22-25), the FGF chimera of the present invention does not demonstrate the absolute heparan sulfate-dependency that is seen for wild type FGF proteins. Therefore, the chimera has FGF activity without the need for the presence of heparan sulfate.

Claim 2 is rejected as being vague and indefinite for the recitation of "wherein said FGF biological activity." Applicants have amended Claim 2 to recite "wherein said chimeric FGF has FGF biological activity." It is believed that this phrase addresses the Examiner's concern.

Claim 4 has been rejected due to recitation of hybridization "under stringent conditions." The Examiner contends that without providing precise hybridization conditions in the claim or specification, the claim is indefinite. Applicants' have amended Claim 4 to recite a percent identity to human FGF-2, combined with a functional limitation, which is believed to be definite. Support for this amendment has been discussed previously herein.

In view of the foregoing amendments and remarks, the Examiner is respectfully requested to withdraw the rejection of Claims 1-18 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1, 3, and 5-7 Under 35 U.S.C. § 102(b)

The Examiner has rejected Claims 1, 3 and 5-7 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Fiddes et al. (U.S. Patent No. 5,604,293). Specifically, the Examiner contends that Fiddes et al. teach a construct of FGF-2 and a signal sequence. The Examiner asserts

that because the present claims encompass transport of the chimera across a lipid bilayer regardless of the direction, inside or outside of the cell, the claimed subject matter is anticipated by Fiddes et al.

Applicants traverse the rejection of Claims 1, 3 and 5-7 under 35 U.S.C. § 102(b). Fiddes et al. merely describe fusing a known secretory peptide (a signal sequence) from human growth hormone onto FGF to mediate secretion of the FGF into the surrounding medium (presumably to facilitate overexpression and purification of the recombinant protein). In making this rejection, the Examiner asserts that the signal sequence from human growth hormone is equivalent to the penetratin peptide of the instant claims because the signal sequence appears to have one of the characteristics of a penetratin (e.g., the ability to transport a protein across a lipid bilayer and out of the cell). However, Applicants respectfully submit that this is an incorrect assertion. A penetratins as claimed in the present chimera functions via a different mechanism compared to normal secretory peptide-mediated membrane traversal, and it is submitted that the signal sequence of Fiddes et al. is not a penetratin. Specifically, Fiddes et al. do not teach the use of a penetratin and therefore, *even if* a signal sequence for human growth hormone has <u>one</u> of the characteristics of a penetratin peptide, it is not sufficient to constitute a teaching of a penetratin-FGF chimeric protein as presently claimed, because the peptides are different.

More particularly, the present specification teaches that a penetratin is capable of transporting itself and a heterologous protein linked to it across a lipid bilayer or any cellular membrane <u>independent of receptor-mediated or other common endocytic pathways</u>. A penetratin peptide <u>does not require a receptor for entry into a cell, nor does it have temperature and energy requirements associated with receptor-mediated or other endocytic biological processes</u> (e.g., the transport can occur at 4°C) (page 20, lines 11-17). In contrast, signal sequences are small peptides that are transported through the endoplasmic reticulum and to the appropriate organelle via recognition by signal recognition particles (SRP) and SRP receptors which enable the transport of a protein to the appropriate organelle and/or out of the cell. Therefore, a signal sequence is a peptide with a specific function that in the case of human growth hormone, causes the protein to be secreted from the cell. While the known signal sequence in the fusion of Fiddes et al. is capable of using cellular machinery to *export* the fusion protein via the common secretory pathway, there is no indication or teaching by Fiddes et al. that this fusion partner can mediate retrograde transport back into the cell, nor would it be expected by those of skill in the art that this common signal sequence could mediate retrograde

transport back into the cell or have the other biological properties of a penetratin peptide (e.g., bidirectional transport, no receptor requirement, no temperature and energy requirements associated with receptor-mediated or other endocytic biological processes).

Therefore, Fiddes et al. do not teach the use of a penetratin peptide as described by the present invention and Fiddes et al. not teach or suggest the claimed chimeric FGF protein. In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 3 and 5-7 under 35 U.S.C. § 102(b).

Double Patenting

The Examiner has stated that if Claim 5 is found to be allowable, that Claim 7 will be objected to as being a substantial duplicate thereof. Applicants have cancelled Claim 5 in favor of Claim 7 and therefore, the Examiner's proposed rejection is moot.

Applicants have attempted to respond to the Examiner's concerns as set forth in the December 31 Office Action. In the event that the Examiner has any questions or concerns regarding Applicants' position, the Examiner is encouraged to contact the below-named agent at (303)863-9700.

Respectfully submitted,

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Date: March 27, 2003